RESEARCH ARTICLE

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Evaluation of *GATA3* and *HER-2* Immunohistochemical Expression as Prognostic Markers in Urothelial Carcinoma of the Urinary Bladder

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Abstract

Objective: Urothelial carcinoma (UC) of the bladder remains a significant clinical challenge due to its high rates of recurrence and progression. Reliable biomarkers to predict tumor behaviour are still needed. *GATA3* and *HER2* have gained attention in this context, but their combined prognostic value has not been fully established. This study aims to evaluate the immunohistochemical expression of *GATA3* and *HER2* in bladder UC and to examine their association with key pathological parameters and patient outcomes. **Methods:** One hundred archival UC specimens (2018–2022) were reviewed. Immunohistochemical staining for *GATA3* and *HER2* was performed and scored using a semi-quantitative H-score. Clinicopathological data and 3-year follow-up information were analysed to assess correlations with recurrence, progression, and survival. **Results:** *GATA3* expression was detected in 80% of tumors, while *HER2* was positive in 25%. Both markers were significantly associated with low-grade histology and non-muscle-invasive disease. Tumors co-expressing *GATA3* and *HER2* showed the most favorable outcomes, including lower recurrence and improved 3-year disease-free survival. In multivariate analysis, *GATA3* retained independent prognostic significance (HR 0.45, p=0.006). *HER2* demonstrated a favorable trend that did not reach statistical significance after adjustment for grade and stage (HR 0.60, p=0.12), suggesting its prognostic signal is partially mediated by tumor differentiation. **Conclusion:** In multivariate analysis, *GATA3* retained independent prognostic significance (HR 0.45, 95% CI 0.25–0.80, p=0.006), while *HER2* did not (HR 0.60, 95% CI 0.35–1.03, p=0.12). However, combined *GATA3*/*HER2* positivity identified a luminal subgroup with significantly better outcomes, supporting the utility of this marker panel for prognostic stratification in early-stage bladder UC.

Keywords: *GATA3*, *HER2*, Urothelial Carcinoma, Immunohistochemistry, Prognosis

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Introduction

Bladder cancer remains a major global health concern and is currently the tenth most frequently diagnosed malignancy worldwide. Most cases are urothelial carcinoma (UC), which accounts for more than 90% of all bladder tumors [1]. Although surgical management and intravesical or systemic therapies have advanced over the years, clinicians still struggle with the high tendency of these tumors to recur and, in a proportion of patients, to progress despite appropriate treatment [2]. This challenge has increased interest in identifying reliable tissue biomarkers that could support diagnosis, help stratify patients more accurately, and possibly guide treatment decisions.

GATA3 is a transcription factor involved in epithelial differentiation and is well-recognized in pathology practice as a sensitive marker for urothelial and breast lineages [3]. Beyond its diagnostic utility, several studies have suggested that its expression pattern may correlate with tumor differentiation and behavior [4, 5]. More recent work has explored its potential links to the immune microenvironment of bladder cancer, with lower expression observed in more aggressive tumors showing immunosuppressive features [6].

HER2, a member of the ERBB family, has been widely studied in breast and gastric cancers, but interest in its role in urothelial carcinoma has increased, especially with the availability of *HER2*-targeted therapies [7, 8]. Experimental studies have shown that *HER2* may contribute to tumor proliferation, migration, and chemoresistance [9]. Its expression, however, appears to vary across UC subtypes and may be more common in tumors with luminal differentiation [10].

Although *GATA3* and *HER2* have been individually studied in bladder cancer [11, 12], there is limited literature examining their combined prognostic value within the same well-defined transurethral resection of bladder

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tumors [TURBT] cohort, particularly in Middle Eastern populations. Therefore, the present study aims to evaluate the diagnostic and prognostic significance of *GATA3* and *HER2* expression in a homogeneous cohort of primary TURBT-derived UC cases, investigate correlations with grade, stage, recurrence, and progression, and clarify technical and biological factors influencing expression rates.

Materials and Methods

This retrospective cohort study included 100 formalin-fixed, paraffin-embedded (FFPE) urothelial carcinoma specimens diagnosed between 2018 and 2022. All specimens were obtained via transurethral resection (TUR). pTa tumors were excluded from this study to focus on tumors with at least lamina propria invasion [pT1] or higher, which carry a higher risk of progression and are more clinically relevant for prognostic biomarker studies. pT3 and pT4 diagnoses were made based on TUR specimens showing deep muscularis propria invasion (pT2) with evident extravesical fat involvement (pT3) or adjacent organ invasion (pT4), as supported by cross-sectional imaging (Computed Tomography and Magnetic Resonance Imaging) and confirmed by multidisciplinary review. For a subset of patients with pT3/T4 disease (n=12, 27% of invasive cases), final pathological staging was based on this combined approach, as cystectomy was not performed in all cases. This represents a potential limitation in staging accuracy, consistent with contemporary bladder cancer guidelines that permit pathological staging from TUR specimens when muscle is present and invasion depth can be assessed.

Clinical data, including age, sex, tumor grade, stage, and muscle invasion, were collected. Follow-up data for at least 3 years were reviewed for recurrence, progression, and overall survival. Exclusion criteria included: non-urothelial tumors, inadequate or autolyzed tissue samples, and incomplete medical records.

Immunohistochemical (IHC) Staining

Immunohistochemical (IHC) staining was performed on formalin-fixed, paraffin-embedded (FFPE) tissue sections (4 μm thick) using an automated stainer (Ventana BenchMark XT, Ventana Medical Systems, Tucson, AZ, USA). Primary antibodies included anti-*GATA3* [clone L50-823 (Biocare Medical, USA) and anti-*HER2*/neu [clone 4B5 Ventana/Roche, Switzerland]. Antigen retrieval was achieved using Cell Conditioning 1 (CC1) buffer (pH 8.5) for 60 minutes. Visualization was carried out using the OptiView DAB IHC Detection Kit (Ventana/Roche), followed by counterstaining. Appropriate positive and negative controls were included in each staining batch to ensure consistency and reliability of staining.

Evaluation of IHC Staining

For *GATA3*, nuclear staining in tumor cells was considered specific, whereas cytoplasmic or membranous reactivity was disregarded. For *HER2*, only distinct membranous staining was considered specific. Staining intensity was graded as 0 (none), 1 (weak), 2 (moderate), or 3 (strong), and the percentage of positive tumor cells was estimated visually. An H-score was then calculated by multiplying intensity (0–3) by the percentage of positive cells (0–100), yielding a total range of 0–300. Tumors with an H-score greater than 10 were considered positive for expression of the respective marker [3, 13–15]. This threshold was selected based on prior published studies in urothelial carcinoma [14, 15] and was validated in our cohort using receiver operating characteristic (ROC) curve analysis for predicting recurrence, which identified an optimal cut-off of H-score >10 (area under the curve: 0.72 for *GATA3*, 0.68 for *HER2*). While this threshold prioritizes sensitivity, we acknowledge that it may include tumors with only focal, weak staining.

IHC Scoring Reproducibility

All slides were independently evaluated by two experienced pathologists who were blinded to the clinicopathological data and patient outcomes. In cases of discrepancy, a consensus score was reached by joint review using a multi-headed microscope. Interobserver agreement for IHC scoring was assessed using Cohen's kappa (κ) statistic, with values interpreted as follows: <0.20 = poor, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = substantial, and >0.80 = almost perfect agreement [16].

Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± standard deviation (SD) or median (range), while categorical variables were expressed as frequencies and percentages. The Chi-square test or Fisher's exact test, as appropriate, was used to evaluate associations between *GATA3* and *HER2* immunoexpression and various clinicopathological parameters, including patient age, sex, tumor grade, pathological stage, and lympho-vascular invasion. Differences in mean values between the two groups were assessed using the independent-samples t-test.

Survival analysis was conducted over a 3-year follow-up period. Overall survival [OS] was defined as the time from the date of surgery to death from any cause or last follow-up, while disease-free survival (DFS) was defined as the time from surgery to the first documented tumor recurrence, metastasis, or last disease-free follow-up. Survival curves were generated using the Kaplan–Meier method, and comparisons between different groups were performed using the log-rank test. To identify independent prognostic factors influencing OS and DFS, a multivariate analysis was performed using the Cox proportional hazards regression model, incorporating variables that showed significance in univariate analysis. Hazard ratios (HR) with corresponding 95% confidence intervals (CI) were calculated. All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant.

Results

Clinicopathological Characteristics

As shown in Table 1, the study included 100 patients with histopathologically confirmed urothelial carcinoma of the urinary bladder. The patients' ages ranged from 42 to 81 years (mean = 61.2 ± 9.4 years). Males represented 72% of cases and females 28%, with a male-to-female ratio of approximately 2.6:1. Low-grade tumors accounted for 63%, while high-grade tumors represented 37% of cases. Non-muscle invasive disease (pT1) was detected in 55% of cases, whereas muscle invasive tumors (pT2–T4) comprised 45%.

During the 3-year follow-up period, 31% experienced recurrence and 24% showed disease progression. The overall 3-year survival rate was 68%, whereas 32% of patients died from disease-related causes.

When excluding the 12 pT3/T4 cases staged without cystectomy confirmation (data not shown), the prognostic associations for *GATA3* and combined marker expression remained directionally consistent, though statistical power was reduced.

Expression of GATA3 and HER2

GATA3 immunoexpression was positive in 80% of cases, characterized by moderate-to-strong nuclear staining. *HER2* positivity was observed in 25% of tumors, showing complete membranous staining in tumor cells, as shown in Figure 1.

Table 1. Clinicopathological Characteristics of the Studied Urothelial Carcinoma Cases

Parameter	Category	No. of cases (n=100)	Percentage (%)
Age	<60 years	58	58
	≥60 years	42	42
Sex	Male	72	72
	Female	28	28
Tumor grade	Low grade	63	63
	High grade	37	37
Tumor stage	Non–muscle- invasive pT1	55	55
	Muscle-invasive (pT2–T4)	45	45
Recurrence	Yes	31	31
	No	69	69
Progression	Yes	24	24
	No	76	76
3-year survival	Alive	68	68
	Dead	32	32

*This table summarizes the demographic and pathological features of the 100 patients included in the study. Most patients were male, and low-grade and non-muscle-invasive tumors were slightly more common. Rates of recurrence, progression, and 3-year survival are also presented.

To assess the robustness of our findings, we performed a sensitivity analysis using a higher threshold for positivity

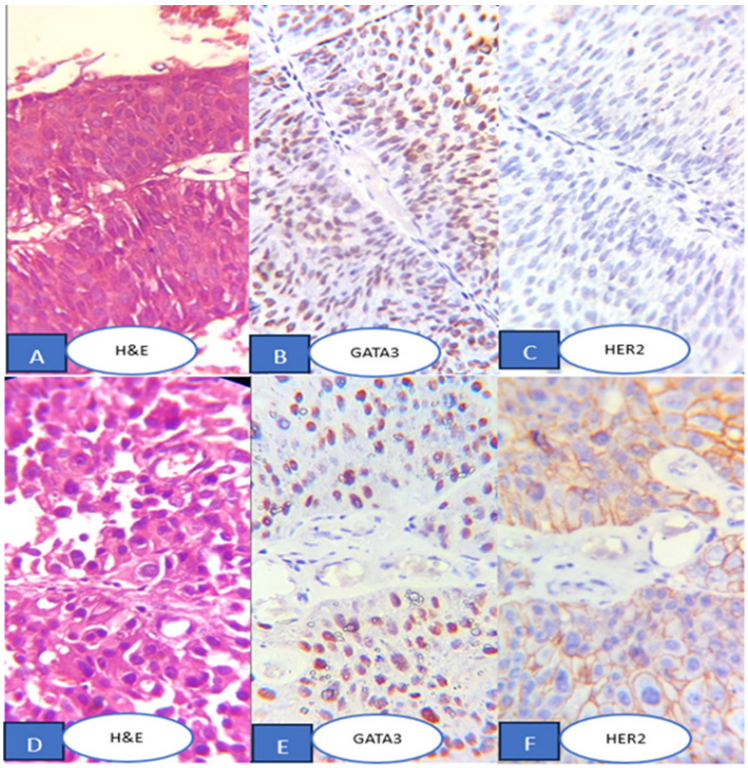

Figure 1. Representative Photographs of Uothelial Carcinoma: A. Low-grade urothelial carcinoma showing delicate papillary structures, mild nuclear atypia, and preserved polarity (H&E, ×40). B. Strong, diffuse nuclear GATA3 immunostaining expression in the same low-grade tumor (×40). C. HER2 immunostaining in this case is negative, with absent membranous labeling (×40). D. High-grade urothelial carcinoma composed of markedly pleomorphic cells with prominent nucleoli, numerous mitoses, and architectural disarray (H&E, ×40). E. GATA3 immunostaining in the high-grade tumor shows only focal to moderate nuclear positivity (×40). F. HER2 immunostaining in the high-grade tumor demonstrates complete strong membranous positivity, consistent with overexpression (×40).

Table 2. Correlation of *GATA3* and *HER2* Expression with Clinicopathological Parameters

Parameter	Category	*GATA3* positive (n=80)	*GATA3* negative (n=20)	χ^2 / p-value	*HER2* positive (n=25)	*HER2* negative (n=75)	χ^2 / p-value
Tumor grade	Low grade	(58) 92%	5 [8%]	$\chi^2 = 9.68$, p = 0.002 *	(19) 30%	(44) 70%	$\chi^2 = 4.76$, p = 0.03 *
	High grade	(22) 58%	(15) 42%		(6) 16%	(31) 84%	
Tumor stage	Non–muscle invasive	(47) 85%	(8) 15%	$\chi^2 = 6.47$, p = 0.01 *	(17) 31%	(38) 69%	$\chi^2 = 3.84$, p = 0.05 *
	Muscle invasive	(33) 62%	(12) 38%		(8) 18%	(37) 82%	
Muscle invasion	Absent	(44) 88%	(6) 12%	$\chi^2 = 8.11$, p = 0.004 *	—	—	—
	Present	(36) 64%	(14) 36%		—	—	—
GATA3 correlation	Positive	—	—	—	(23) 29%	(57) 71%	$\chi^2 = 7.65$, p = 0.006 *
	Negative	—	—	—	(2) 10%	(18) 90%	

*This table details how marker positivity correlates with tumor grade, stage, and muscle invasion. Both *GATA3* and *HER2* were significantly more common in low-grade and non-muscle-invasive tumors. A strong association was also observed between *GATA3* and *HER2* co-expression. χ^2, chi-square test.

(H-score >100, representing at least moderate staining in >33% of cells). Using this stringent cut-off, *GATA3* positivity decreased to 54% (from 80%), and *HER2* positivity decreased to 12% (from 25%). The prognostic associations for both markers remained statistically significant for disease-free survival (*GATA3*: HR 0.52, 95% CI 0.31–0.87, p=0.01; *HER2*: HR 0.58, 95% CI 0.34–0.99, p=0.04), though with wider confidence intervals due to reduced sample size in positive groups. The combined *GATA3*-positive/*HER2*-positive group continued to show the most favorable outcomes, supporting the validity of our primary findings.

Correlation of GATA3 Expression with Clinicopathological Parameters

GATA3 expression showed statistically significant correlations with multiple parameters (Table 2). It was significantly higher in low-grade tumors (92%) compared with high-grade ones (58%) (χ^2 = 9.68, P = 0.002). Similarly, *GATA3* positivity was more frequent in non-muscle invasive cases (85%) than in invasive tumors (62%) (χ^2 = 6.47, P = 0.01). A significant

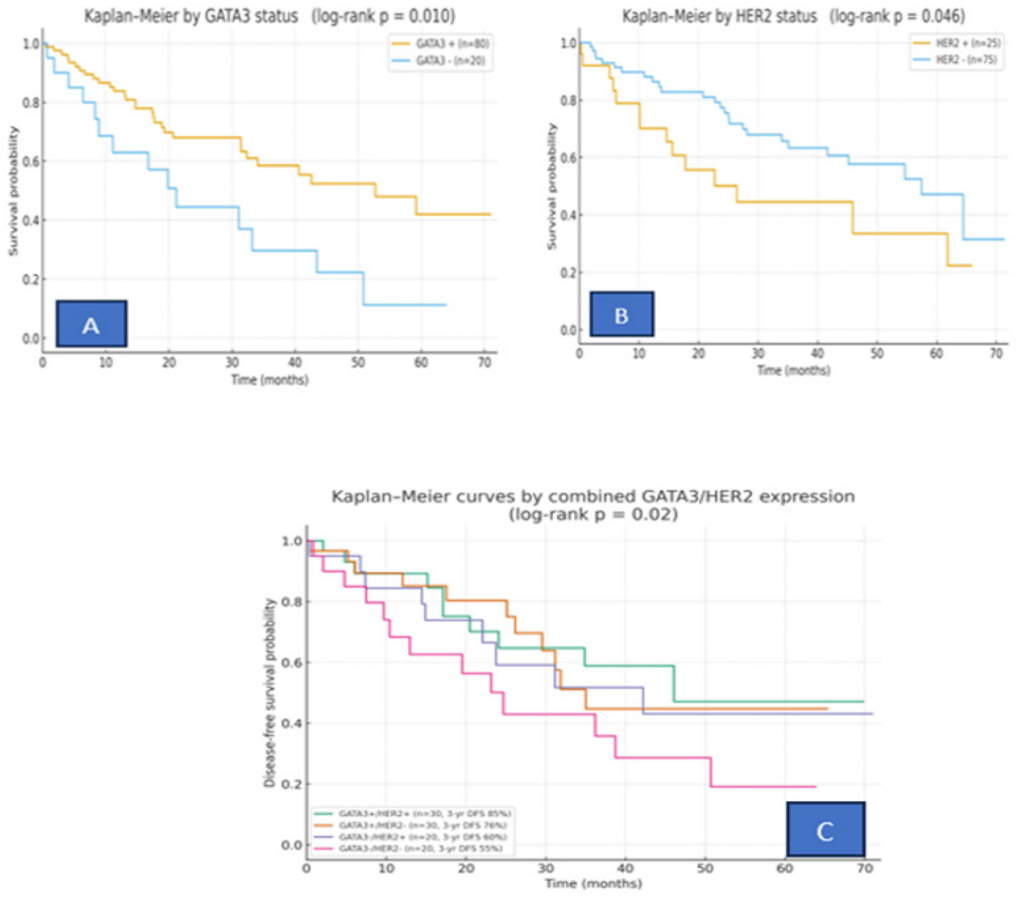

Figure 2. A, B, C. Kaplan–Meier Survival Curves Illustrating 3-Year Disease-Free Survival in Relation to *GATA3* and *HER2* Expression. Tumors positive for either marker show improved outcomes, with the *GATA3*-positive/*HER2*-positive group exhibiting the most favorable survival profile.

Table 3. Combined *GATA3* and *HER2* Expression and Its association with 3-Year Outcomes

Expression pattern	Recurrence (%)	Progression (%)	3-year DFS (%)	χ^2	p-value (log-rank)
GATA3-positive /*HER2*-positive	18%	10%	85%	8.73	0.02*
GATA3-positive /*HER2*-negative	24%	18%	76%		
GATA3-negative/*HER2*-positive	40%	33%	60%		
GATA3-negative/*HER2*-negative	45%	42%	55%		

*This table compares recurrence, progression, and disease-free survival across the four expression groups. The *GATA3*-positive/*HER2*-positive subgroup demonstrates the most favorable clinical course, while double-negative tumors show the highest rates of recurrence and progression. DFS, disease-free survival; χ^2, chi-square test.

inverse association was also found with muscle invasion (P = 0.004). No significant correlation was observed with patient sex or age. These findings confirm that *GATA3* expression is linked to well-differentiated, less aggressive tumors.

Correlation of HER2 Expression with Clinicopathological Parameters

As summarized in Table 2, *HER2* overexpression was observed in 30% of low-grade versus 16% of high-grade tumors (P = 0.03). *HER2* positivity was slightly more frequent in non-muscle-invasive tumors (31%) than in invasive ones (18%) (P = 0.05). A strong positive correlation was observed between *HER2* and *GATA3* expression (P = 0.006), indicating that *HER2* tends to co-express with luminal differentiation markers.

Combined GATA3/HER2 Expression and Clinical Outcomes

As detailed in Table 3& Figure 2, the combined expression of *GATA3* and *HER2* had significant prognostic implications. Patients with dual positivity (*GATA3*- positive/*HER2*-positive) demonstrated the lowest recurrence rate (18%) and progression rate (10%), with an estimated 3-year disease-free survival (DFS) of 85%. By contrast, the double-negative group (*GATA3*-negative/*HER2*-negative) had the highest recurrence (45%), progression (42%), and lowest DFS (55%) (log-rank P = 0.02).

Intermediate survival was seen in single-positive groups.

The multivariate Cox models (Supplementary Figure 1) indicate that higher histologic grade and muscle-invasive stage are independent adverse prognostic factors for both disease-free survival and overall survival. *GATA3* immunopositivity is independently associated with a reduced hazard of recurrence and death (DFS HR 0.45, 95% CI 0.25–0.80, p=0.006; OS HR 0.50, 95% CI 0.28–0.90, P=0.02), consistent with *GATA3* as a luminal/differentiation marker linked to better prognosis. *HER2* immunopositivity trends toward a protective effect (HRs 0.60 and 0.70 for DFS and OS, respectively) but does not reach statistical significance after adjustment for grade and stage suggesting that *HER2*'s prognostic signal is partly mediated by tumor differentiation and stage. Age modestly increases the hazard for OS and DFS per year. These results support reporting *GATA3* as an independent prognostic marker and considering *HER2* within combined marker panels or in larger cohorts to clarify independent predictive value.

Discussion

This study assessed the expression of *GATA3* and *HER2* in 100 cases of bladder urothelial carcinoma and examined their relationship with tumor characteristics and clinical outcomes. The finding of 63% low-grade tumors in the absence of pTa cases is explained by the inclusion of low-grade invasive tumors (pT1), which are well-documented in the literature. Not all invasive tumors are high-grade; a subset of pT1 tumors retains low-grade cytology and architecture. Our cohort reflects this heterogeneity, which is important for evaluating biomarkers across the differentiation spectrum.

GATA3 expression was detected in 80% of tumors, while *HER2* positivity was observed in 25%. As expected, both markers were more frequently expressed in low-grade and non-muscle-invasive tumors. Their combined positivity identified a subgroup of patients who experienced fewer recurrences and had better 3-year disease-free survival, suggesting a link between co-expression and a more favorable clinical course.

While *GATA3* is a sensitive urothelial marker, its expression is not universal and can be reduced in poorly differentiated, high-grade, or muscle-invasive tumors. Our 80% positivity rate is within the reported range (70–90%) and aligns with studies showing decreased *GATA3* expression in aggressive subtypes [15]. The slightly higher positivity in our cohort may reflect differences in antibody clones, scoring approaches, or the distribution of tumor stages. Naga et al. [17] similarly reported strong *GATA3* expression in luminal-type tumors with relatively low proliferative activity, supporting its association with more differentiated lesions.

The *HER2* positivity rate in our study (25%) aligns with values from several recent reports, including Allegretti et al. [18] and Scherrer et al. [4], although variability among studies remains considerable. This variability likely stems from differences in scoring thresholds, tumor composition, and technical factors. Some authors have highlighted an association between *HER2* expression and luminal differentiation, while others have linked high *HER2* expression to more aggressive behavior [4, 18]. These conflicting observations may reflect biological heterogeneity within *HER2*-positive tumors, where *HER2* expression in papillary, well-differentiated lesions likely signifies a different biological context than in poorly differentiated or basal-type tumors.

Recent molecular analyses further support the idea that *HER2*-positive bladder carcinomas often show a luminal phenotype. Sheikh et al. [19] noted that *HER2*-expressing

tumors commonly co-express markers such as *GATA3* and FOXA1, and that these tumors exhibit distinct metabolic characteristics. Differences in study populations and treatment protocols may explain why some studies unlike ours have found *HER2* overexpression to be associated with worse outcomes [9, 20]. Importantly, our multivariate analysis showed that *HER2* did not retain independent prognostic significance after adjustment for grade and stage, suggesting that its prognostic signal is partially mediated by tumor differentiation. This may explain why some studies unlike ours have found *HER2* overexpression to be associated with worse outcomes when examined in univariate analysis alone [9, 20].

One important point to consider is that our cohort consisted predominantly of early-stage tumors managed conservatively. This may partly explain why *HER2* positivity did not show the adverse prognostic associations reported in more advanced disease or in cohorts treated with systemic therapy. Geographic and ethnic variability may also contribute, as highlighted by studies demonstrating considerable differences in *HER2* amplification patterns across populations [9, 21].

Despite these strengths, our study has several limitations. It is retrospective and single-center, which restricts generalization. The sample size, although adequate for detecting major associations, may not capture the full heterogeneity of *HER2*-positive tumors. A major limitation of this study is the absence of molecular confirmation of *HER2* status by fluorescence in situ hybridization (FISH) or chromogenic in situ hybridization (CISH). While IHC is a practical screening tool widely used in clinical practice, it cannot definitively distinguish between true gene amplification and protein overexpression without amplification. The correlation between IHC and FISH in urothelial carcinoma is imperfect, and our *HER2* positivity rate of 25% may include cases with protein overexpression without corresponding gene amplification. Future studies should integrate IHC with molecular testing to validate our findings and clarify the biological and prognostic significance of *HER2* expression in this context.

Furthermore, the chosen cut-off for positivity (H-score >10) is relatively low and may include tumors with only focal, weak staining. While this approach increases sensitivity which is valuable for screening purposes it may reduce specificity. However, our sensitivity analysis using a more stringent cut-off (H-score >100) confirmed the prognostic associations, suggesting that our findings are not solely driven by the threshold choice. Nevertheless, external validation using alternative scoring criteria is warranted.

An additional limitation relates to tumor staging: for a subset of pT3/T4 cases (n=12), staging was based on TUR specimens combined with imaging rather than cystectomy pathology, which could introduce staging inaccuracies. However, the distribution of stages in our cohort (55% pT1, 45% pT2-T4) reflects real-world practice where not all patients undergo immediate cystectomy.

Recommendations: Future multicenter prospective studies with longer follow-up are recommended to confirm the prognostic value of *GATA3* and *HER2* co-expression. Standardization of *HER2* scoring and integration of IHC with molecular profiling (FISH/CISH) could further clarify their biological and therapeutic significance. Prospective studies should establish the optimal *HER2* testing algorithm for prognostic and potentially predictive purposes in bladder cancer.

Overall, this study demonstrates that *GATA3* and *HER2* are frequently expressed in urothelial carcinoma and tend to occur in tumors with lower grade and non-muscle-invasive stage. Patients whose tumors expressed both markers had noticeably better disease-free survival and lower recurrence and progression rates. Among the two markers, *GATA3* showed independent prognostic value in multivariate analysis (HR 0.45, 95% CI 0.25–0.80, p=0.006), while *HER2* demonstrated a positive but non-significant trend (HR 0.60, 95% CI 0.35–1.03, p=0.12). The key finding is that co-expression of both markers identifies a luminal-like subgroup with significantly better outcomes, suggesting that *HER2*'s prognostic signal is context-dependent and linked to tumor differentiation. These findings support the usefulness of *GATA3* as a prognostic marker in bladder UC and suggest that evaluating *HER2* alongside it may provide additional context, particularly for defining luminal-type tumors. The prognostic value of *HER2* alone appears limited in multivariate analysis, but its co-expression with *GATA3* refines risk stratification. Larger, multi-institutional studies incorporating molecular confirmation of *HER2* status would help clarify its precise prognostic role and expand its potential utility in therapeutic decision-making.

Author Contribution Statement

Mona S. Mohammed: Conceptualization, methodology design, data curation, immunohistochemical analysis, manuscript writing – original draft preparation. Nehal S. Abouhashim: Supervision, review, and editing of the manuscript, validation, and final approval of the version to be published. Mariem A. Elfeky: Data collection, histopathological examination, statistical analysis, and visualization.

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Data Availability

The data supporting the outcome of this research work have been reported in this manuscript and the supplementary material file.

Ethical Declaration

Ethical approval was obtained from the Zagazig University Institutional Review Board [ZU-IRB #1581/2-Sep-2025].

Conflict of Interest

The authors declare no conflicts of interest.

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